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TITLE: Biomarkers for Early Detection of Clinically Relevant Prostate Cancer. A Multi-Institutional Validation Trial

PRINCIPAL INVESTIGATOR: Jesse McKenney, MD

CONTRACTING ORGANIZATION: Cleveland Clinic Foundation
Cleveland, OH 44195

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14. ABSTRACT For men diagnosed with early stage prostate cancer a critical need exists for molecular assays that accurately distinguish aggressive prostate cancer from those cancers that will not cause harm if left untreated. In this project, we are assessing three different panels of established molecular biomarkers for their ability to distinguish aggressive cancers from indolent cancers. We have established agreements with three commercial companies to analyze their biomarker platforms in our multi-center, prospectively accrued prostate cancer active surveillance cohort – the Canary Prostate Active Surveillance Study (PASS). We are in the process of evaluating these three biomarker panels in tissue, blood, and urine samples with well annotated clinical and pathologic data collected as part of PASS. We are conducting rigorous statistical evaluation to demonstrate the utility and performance of biomarkers in clinical practice to predict aggressive disease. The accuracy of each biomarker for predicting short- and long-term progression will be characterized with time dependent receiver operating characteristic curves. The successful clinical validation of biomarkers that offer substantially improved predictive and prognostic accuracy should bring extraordinary potential to improve the care of prostate cancer patients.					
15. SUBJECT TERMS Prostate cancer, active surveillance, biomarkers, validation					
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1. INTRODUCTION

Although prostate-specific antigen (PSA) testing and the resulting treatment of prostate cancer (PCa) is likely responsible for some of the 44% decrease in prostate cancer mortality witnessed in the United States since 1992, the detection of low risk tumors has increased. The majority of prostate cancers currently diagnosed are low risk tumors for which there is substantial evidence that the cancer will not cause harm if left untreated. However, enough uncertainty remains in accurately identifying which tumors will not cause harm to a patient that many low risk cancers are still treated, resulting in so-called overtreatment. To reduce this overtreatment, while still diagnosing aggressive high risk tumors early enough that they can be successfully treated, there is a critical need for molecular assays that accurately distinguish more aggressive disease from cancers that will not cause harm. The goal of this project is to perform rigorous clinical validation of established biomarkers in order to improve the accuracy of risk assessment and distinguish aggressive from indolent disease in men with apparently low-risk disease by standard clinical variables. We are evaluating multiple established and analytically validated quantitative molecular biomarkers to predict PCa progression in a multi-center active surveillance cohort with high-quality biospecimens. We aim to unlink the diagnosis of PCa with immediate treatment, thus addressing the overtreatment issue and economic, physical, and emotional burdens of PCa diagnoses. The results have promise to change the standard of care in the treatment of the majority of newly diagnosed PCa with near term impact due to the availability of the biomarkers and execution in an established, prospective cohort of men undergoing AS.

2. KEYWORDS

Prostate cancer; active surveillance; progression; aggressive disease; central pathology review; biomarkers; prediction models; PCA3; TMPRSS2:ERG; kallikreins; 4KScore; OncotypeDX;

3. ACCOMPLISHMENTS

What were the major goals and objectives of the project?

We hypothesize that biomarkers of disease aggressiveness and prognosis can be interrogated in low risk prostate cancer (PCa) and that these biomarkers will better detect clinically relevant PCa in asymptomatic patients, thus distinguishing aggressive from indolent disease and immediately impacting both the initial choice of therapy and decision-making during AS. The objective of the study is to utilize analytically validated assays that take into account tumor heterogeneity to measure biomarkers in specimens that were collected in a non-invasive manner.

The major goals of the project, as stated in the scope of work, are:

1. Collection of specimens and clinical data. (Coordinated by FHCRC)

Milestone 1. Completion of a minimum of three years of follow-up with high-quality data and specimen collection. Due: 12/30/2016

2. Analysis of scientific aim 1: Validate a panel of tissue-based biomarkers to determine the presence of or progression to aggressive disease. (Lead site: FHCRC)

Milestone 2. Execute collaboration agreement with GHI. Due 12/30/2014
COMPLETED.

Milestone 3. Tissue blocks identified for analysis. Due: 12/30/2015

Milestone 4. Oncotype DX validation complete in PASS cohort. Due 12/30/2016

Milestone 5. Manuscript submission of Oncotype DX validation. Due 9/30/2017

3. Analysis of scientific aim 2: Evaluate a panel of four-kallikrein plasma-based markers to determine the presence of or progression to clinically relevant prostate cancer. (Lead site: FHCRC)

Milestone 6. Execute collaboration agreement with OPKO. Due 3/30/2015
COMPLETED.

Milestone 7. Plasma samples identified for analysis. Due 12/30/2015 **COMPLETED**

Milestone 8. OPKO 4K Score validation complete in PASS cohort. Due 9/30/2016

Milestone 9. Manuscript submission of 4KScore validation. Due 9/30/2017

4. Analysis of scientific Aim 3: Confirm the ability of PCA3 mRNA concentrations in urine, alone or in combination with TMPRSS2:ERG mRNA. (Lead site: FHCRC)

Milestone 10. Urine specimens identified for analysis. Due 12/30/2014
COMPLETED

Milestone 11. PCA3 and TMPRSS2:ERG validation complete in PASS cohort. Due 12/30/2015

Milestone 12. Manuscript submission of PCA3 and TMPRSS2:ERG validation. Due 9/30/2017

5. Central pathology review of PASS biopsy and RP slides. (Lead site: CCF)

Milestone 13. Completion of Central Pathology Review for biopsy-driven endpoints. Due: 12/30/2016

6. Translation of biomarkers into clinical practice. (Lead sites: FHCRC and CCF)
Milestone 14. Construction of integrated model of biomarkers for the prediction of progression in the PASS cohort. Due 9/30/2017
Milestone 15. Manuscript submission of integrated model for prediction of progression. Due 9/30/2017

What was accomplished under these goals?

In this first year of funding, we successfully completed collaboration agreements between PASS and our three industry partners (Genomic Health, Inc., OPKO Diagnostics, and Hologic/Gen-Probe). We provided copies of these fully executed agreements with our earlier quarterly reports. Plasma specimens were delivered to OPKO, Inc., and analyses of the assay results are underway at FHCRC. Urine specimens (N=1,041) were delivered to Hologic/Gen-Probe, and analyses of the assay results are underway at FHCRC. Under the direction of Dr. McKenney, the Central Pathology review system has been implemented. With this system in place, diagnostic slides are scanned and made available for review on a web-based, multi-site pathology scoring system. All of our stated goals were met according to the project timeline, and are expected to proceed as expected.

What opportunities for training and professional development did the project provide?

Nothing to report. This grant does not provide for training or professional development activities.

How were the results disseminated to communities of interest?

Nothing to report. In the first year of funding, we are still collecting specimens, running assays, and analyzing results. At this time we are not yet ready to disseminate results.

What do you plan to do during the next reporting period to accomplish the goals and objectives?

In the next year of funding, we will continue collecting follow-up data on the 1,000 PASS Study participants. We have finalized the specimen protocol with Genomic Health for the Oncotype Dx tissue processing, and anticipate that we will begin transferring specimens to Genomic Health by 12/30/2015. We expect to complete analyses of the 4K Score assay data in the coming year. We also aim to have completed our analysis to validate PCA3 and TMPRSS2:ERG assays in PASS urine specimens.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

We anticipate that the successful clinical validation of biomarkers that offer substantially improved predictive and prognostic accuracy would bring extraordinary potential to improve the care of PCa patients. Specifically, those men with clinically low-risk tumors that can be confirmed as truly low-risk with greater accuracy could be spared the cost and quality-of-life impact of invasive diagnostic and therapeutic maneuvers. Conversely, those men with apparent low-risk disease who in fact harbor higher-risk tumors or have the potential to develop lethal disease will be identified, thus avoiding under-treatment. Such a paradigm shift in PCa care would yield near-term changes in the PCa treatment landscape, greatly improving the cost-benefit calculations for population-level PCa screening efforts and reducing the overtreatment of disease.

What was the impact on other disciplines?

Nothing to report in this period, although we expect that statistical techniques being developed will be utilized to evaluate biomarker performance in many diseases other than prostate cancer.

What was the impact on technology transfer?

This project involves evaluation and validation of commercial biomarker panels that have not previously been used in the active surveillance setting. While we do not expect a direct impact on technology transfer, there should be a large impact on the commercial use of the molecular diagnostics.

What was the impact on society beyond science and technology?

Successful execution of this project should transform the clinical management of prostate cancer in several ways. First, if patients and their physicians have a reliable and valid estimate of the risks of disease progression and harm, then more might opt for surveillance, thereby reducing the risks of overtreatment and its attendant substantial costs and morbidity. Such improved accuracy would allow men to be selected more appropriately and with greater confidence for surveillance rather than immediate treatment. Second, a proportion of men initially choosing active surveillance eventually opt for primary curative treatment even with no objective measures of clinical progression, presumably due to patient/provider anxiety. Increasing patient and provider confidence in risk assessments would presumably lead to increased adherence to active surveillance, further decreasing overtreatment. Third, a marker panel with high accuracy for progression on active surveillance will influence the regimen of clinical re-assessment, such that those men with particularly low-risk disease might be eligible for a less intensive surveillance protocol with fewer repeated prostate biopsies, reducing the use of the most invasive, and risky, component of a typical surveillance regimen. Fourth, the proposed markers might also facilitate treatment planning for men not currently on surveillance. For example, a man with apparently low-risk disease but a significantly adverse biomarker panel would have an increased risk of occult high grade disease and perhaps should undergo staging lymphadenectomy at time of prostatectomy, a procedure which might not routinely be performed for low risk disease. Lastly, the public health impact of a validated biomarker panel will be substantial, as the costs of initial curative therapy for prostate cancer

accounts for \$2-3 billion annually. Approximately half of the new diagnoses are low risk cancers and candidates for active surveillance, and accurate determination of who may benefit from curative therapy, while sparing the majority, would have immediate economic impact.

5. CHANGES / PROBLEMS

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:

- **Significant changes in use or care of human subjects:** No significant changes in the use or care of human subjects. The Fred Hutchinson Cancer Research Center has approved the study activities through 5/29/2016 under IR file number 8271. The USAMRMC Office of Research Protections Human Research Protection Office reviewed and approved the project under HRPO log number A-18320 on 01/07/2015 and a continuing review was submitted to HRPO on 6/22/2015 and receipt was acknowledged on 07/09/2015.
- **Significant changes in use or care of vertebrate animals:** Nothing to report.
- **Significant changes in use of biohazards and/or select agents:** Nothing to report.

6. PRODUCTS

Publications, conference papers, and presentations

Nothing to report at this time.

Journal publications

Nothing to report.

Books or other non-periodical, one-time publications

Nothing to report.

Other publications, conference papers, and presentations

Nothing to report.

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

As part of this project we continue to maintain a large biospecimen repository with associated clinical and demographic data, which serves as a rich resource for the scientific community. In the coming years of this award we anticipate scientific results, validated diagnostics, and prediction models that should make an impact on the clinical management of patients with prostate cancer.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Daniel Lin, MD
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	ORCID: 0000-0002-2135-1534
Nearest person month worked:	2 person months
Contribution to Project:	As Principal Investigator, Dr. Lin oversees the execution of the project, including interactions with industry collaborators and the FDA. He directs overall scientific activities including data collection, interpretation, and manuscript preparation. Dr. Lin takes a central role in the analysis of all data from the project, collaborating with the other investigators on manuscript preparations.
Funding Support:	N/A

Name:	Jesse McKenney, MD
Project Role:	Principal Investigator of Partner Award
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1 person months
Contribution to Project:	Dr. McKenney is the lead pathologist for this project, overseeing all aspects of the central pathology review. He has worked on development of the Centralized Pathology Review system, and leads the group of study pathologists who review all endpoints for PASS participants. He ensures that pathologic review is timely and follows project guidelines.
Funding Support:	N/A

Name:	Hilary Boyer
Project Role:	Research Scientist
Researcher Identifier (e.g. ORCID ID):	N/A

Nearest person month worked:	4 person months
Contribution to Project:	Ms. Boyer works under the direction of Dr. Newcomb to receive, annotate, and track PASS specimens from the Central Repository. Ms. Boyer is responsible for pulling, tracking, and documenting specimens sent to collaborating sites and coordinates all shipping activities. She also assists in specimen and clinical data QA and QC, in monitoring study progress, and in preparing reports for study investigators.
Funding Support:	N/A

Name:	Marshall Brown, MS
Project Role:	Statistical Research Associate
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	4 person months
Contribution to Project:	Mr. Brown works under the supervision of Dr. Zheng, Mr. Brown performs data analyses, study reports, data interpretation and manuscript preparation.
Funding Support:	N/A

Name:	Anna Faino, MS
Project Role:	Statistical Research Associate
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	4 person months
Contribution to Project:	Ms. Faino works under the supervision of Dr. Zheng and is responsible for the extensive data analysis involved in this project. She participates in study consultation with project investigators and the data operations group on data and database forms. Under Dr. Zheng's supervision she performs data analyses, data interpretation and manuscript preparation.
Funding Support:	N/A

Name:	Suzanne Kolb
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Project Role:	Project Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	5 person months
Contribution to Project:	Ms. Kolb works under the direction of Drs. Lin and Newcomb to fulfill daily fiscal and administrative functions of the program. She monitors subaward budgets, provides logistical support. Ms. Kolb works closely with the PASS Deputy Director to maintain IRB files, material transfer agreements, and other regulatory documents as well as tracking project timelines and deliverables.
Funding Support:	N/A

Name:	Lisa Newcomb, PhD
Project Role:	Deputy Director
Researcher Identifier (e.g. ORCID ID):	ORCID: 0000-0003-3505-3754
Nearest person month worked:	6 person months
Contribution to Project:	Dr. Newcomb facilitates the day-to-day operations of all aspects of the research, interfacing with the PASS Study to ensure high quality data and specimens. She works closely with Dr. Lin and all investigators and collaborators in the execution of the project. Dr. Newcomb is responsible for specimen selection, management of the acquisition and distribution of specimens from the biorepository, as well as overseeing regulatory requirements and supervising study staff.
Funding Support:	N/A

Name:	Maria Tretiakova, MD, PhD
Project Role:	Co-investigator, Pathologist
Researcher Identifier (e.g. ORCID ID):	ORCID: 0000-0002-0819-9638
Nearest person month worked:	2 person months
Contribution to Project:	Dr. Tretiakova is responsible for reviewing slides of

	prostate needle biopsies and characterizing the pathologic parameters such as Gleason score and amount of cancer. She is also working with co-investigators at FHCRC and Cleveland Clinic on study design, data analysis, and interpretation.
Funding Support:	N/A

Name:	Lawrence True, MD
Project Role:	Pathologist
Researcher Identifier (e.g. ORCID ID):	0000-0002-8621-9569
Nearest person month worked:	1 person month
Contribution to Project:	Dr. True is responsible for reviewing slides of prostate needle biopsies and characterizing the pathologic parameters such as Gleason score and amount of cancer. He is working with co-investigators at FHCRC and Cleveland Clinic on study design, data analysis, and interpretation.
Funding Support:	N/A

Name:	Richard Westcott
Project Role:	Programmer
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	2 person months
Contribution to Project:	Mr. Westcott is responsible for customizing and maintaining the PASS study database as well as the central pathology review system. This includes creation of custom slide views, annotation forms, and reports to facilitate the pathology review workflow and collect and monitor the pathology review data. Mr. Westcott also prepares reports for investigators and the PASS team.
Funding Support:	N/A

Name:	Yingye Zheng, PhD
Project Role:	Co-investigator, Biostatistician
Researcher Identifier (e.g. ORCID ID):	ORCID: 0000-0002-3078-4200

ORCID ID):	
Nearest person month worked:	2 person months
Contribution to Project:	Dr. Zheng is responsible for all statistical aspects of this project, including design and analysis. She consults with investigators on study designs and necessary study design modifications if necessary during the course of the study. She ensures that appropriate data items are collected for valid data analyses and QA/QC to be conducted to ensure high quality of clinical and assay data. She also supervises the SRA in data analyses and interpretation of study data.
Funding Support:	N/A

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes. Listed below are changes in the other support for senior and key personnel. Please note: none of these changes impacts effort on the project.

LIN, D.

New Funding:

R01 (Rubin/Lin) 8/1/14 – 7/31/19 1.2 cal months
NIH \$74,497 (subcont.)
Precision Medicine Approach to Prostate Cancer Active Surveillance

PASS-GHI (Genomic Health, Inc.) 07/15/14 – 12/31/19 .36 cal months

Subaward from Fred Hutchinson CRC \$208,375
Molecular Markers for the Prediction of Disease Progression in Men with Clinically Localized Prostate Cancer on Surveillance in the Canary Prostate Active Surveillance Study

U01 CA086402-15S2 07/01/14 – 06/30/15 0.1 cal months
NIH/NCI (UTHSCSA – PI: I. Thompson) \$29,126
Biomarkers and Clinical Parameters Associated with Gleason Score Upgrading

R01 CA184075 (Wright) 4/1/15 – 3/31/19 0.6 cal months
NIH \$92,612
PALS: Prostate Cancer Active Lifestyle Study

Funding Ended:

R01 CA131255-05 (Lin/Knudsen) 7/23/09 – 5/31/15 .24 cal months
NIH/NCI \$482,359

In vivo Effects of Sulforaphane Supplementation on Normal Human Prostate

R01 AG037603 (Page) 7/01/10 – 6/30/15 .24 cal months
 NIH/NIA \$218,120
 Dose-response Relationships between Circulating and Intraprostatic Androgens in Men

P50 CA97186-11 (Nelson) 9/1/13 – 8/31/18 0.6 cal months
 NIH/NCI \$144,123
 Pacific Northwest Prostate Cancer SPORE
 Project 1: Genetic Susceptibility to Clinically Aggressive Prostate Cancer (Stanford)

Protocol #553 (Montgomery/Lin) 05/02/05 - 05/01/14 1.2 cal months
 Department of Veterans' Affairs \$5,000
 VA Cooperative Studies Program: Chemotherapy After Prostatectomy (CAP) For High Risk Prostate Carcinoma: A Phase III Randomized Study

W81XWH-10-PCRP-IA (Carroll) 6/15/11 – 6/14/14 .60 cal months
 DOD \$18,314
 Predicting Prostate Cancer Progression at Time of Diagnosis

MCKENNEY, J.

New Funding:

R01 (Rubin/Lin) 8/1/14 – 7/31/19 1.2 cal months
 NIH \$21,961 (subcont.)
 Precision Medicine Approach to Prostate Cancer Active Surveillance

TRETIKOVA, M.

New Funding:

Prostate Cancer Foundation (Nelson) 12/24/14-12/24/16 0.6 cal months
 Subaward from Fred Hutchinson CRC \$400,000
 Eradicating Lethal Micrometastatic Cancer Through High Intensity Short Course AR Suppression

W81XWH-14-2-0183 (Morrissey) 9/30/14-9/29/17 .96 cal months
 DOD \$173,181
 Prostate Cancer Biorepository Network

TRUE, L.

New Funding:

W81XWH-14-2-0183 (Morrissey) 9/30/14-9/29/17 .96 cal months
 DOD \$173,181
 Prostate Cancer Biorepository Network

W81XWH-15-1-0430 (Nelson)	7/1/15-6/30/18	.24 cal
months		
DOD	\$16,630	
Minimally-Invasive Assessments of Prostate Cancer Molecular Heterogeneity to Direct Precision Therapy		

PC 130652 (Tomlins)	9/30/14-9/29/17	.94 cal
months		
DOD	\$22,148	
Clonal evaluation of prostate cancer by ERG/SPINK1 status to improve prognosis prediction		

Funding Ended:

P01 CA085859-09 (Vessella)	08/01/09 - 07/31/15	1.8 cal
months		
NIH/NCI	\$1,786,571	
Mechanisms and Markers of Prostate Cancer Metastases, Core A: Tissues/Sera/Models		

U01 CA111244-06 (Liu)	09/22/10 - 06/30/15	.24 cal months
NIH/NCI	\$1,411,642	
Early Detection Research Network: Biomarker Developmental Laboratories		

ZHENG, Y.

New Funding:

R01 CA181605 (Nelson)	1/1/2014 – 12/31/2018	0.6 cal months
NIH/NCI	\$137,920	
Non-Invasive Biomarkers for Diagnosing Clinically Significant Prostate Cancer		

R01 CA195798 (Hsu)	09/01/2015 – 08/31/2019	1.2 cal months
NIH/NCI	\$250,000	
Statistical Methods for Genetic Epidemiologic Studies		

Funding Ended:

R01 CA170122 (Newcomb)	09/12/12-08/31/15	0.6 cal months
NIH/NCI	\$661,233	
Development of a Comprehensive Model for Colorectal Cancer Risk Prediction		

R01 CA176272 (Newcomb/Chan)	04/01/13-03/31/17	0.6 cal months
NIH/NCI	\$1,652,932	
Molecular Correlates of Outcomes in Clinical Trials of Colorectal Cancer		

What other organizations were involved as partners?

Organization Name: University of Washington

Location of Organization: Seattle, WA

Partner's contribution to the project:

Facilities: Staff (Drs. Lin, True, Tretiakova) used facilities provided by the University of Washington for pathology review and office space.

Collaboration: University of Washington personnel provide expertise in pathology (Drs. Tretiakova and True) and study oversight (Dr. Newcomb).

Organization Name: Cleveland Clinic

Location of Organization: Cleveland, OH

Partner's contribution to the project:

Facilities: Dr. McKenney uses facilities provided by the Cleveland Clinic for central pathology review.

Collaboration: Dr. McKenney provides expertise for central pathology review.

Organization Name: Genomic Health, Inc.

Location of Organization: Redwood City, CA

Partner's contribution to the project:

Collaboration: Genomic Health, Inc. has agreed to run Prostate Oncotype Dx assays free of charge and discussed design of project.

Organization Name: OPKO Diagnostics

Location of Organization: Miami, FL

Partner's contribution to the project:

Collaboration: OPKO Diagnostics has run the blood kallikrein assays free of charge and discussed design of project.

Organization Name: Hologic GenProbe

Location of Organization: San Diego, CA

Partner's contribution to the project:

Collaboration: Hologic GenProbe has run the PCA3 and TMPRSS2:ERG urine marker assays free of charge.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

For this project, Dr. Daniel Lin is the initiating PI and Dr. Jesse McKenney is the partnering PI. Drs. Lin and McKenney are independently submitting a duplicate annual project report, with tasks clearly marked with the responsible PI and research site as requested.

QUAD CHARTS: Not applicable.

9. APPENDICES: None.